Review

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Behind the scenes of EQA – characteristics, capabilities, benefits and assets of external quality assessment (EQA)

Part I – EQA in general and EQA programs in particular

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Abstract: This is the first in a series of five papers that detail the role and substantial impact that external quality assessment (EQA) and their providers‘ services play in ensuring *in-vitro* diagnostic (IVD) performance quality. The aim is to give readers and users of EQA services an insight into the processes in EQA, explain to them what happens before EQA samples are delivered and after examination results are submitted to the provider, how they are assessed, what benefits participants can expect, but also who are stakeholders other than participants and what significance do EQA data and assessment results have for them. This first paper presents the history of EQA, insights into legal, financing and ethical matters, information technology used in EQA, structure and lifecycle of EQA programs, frequency and intensity of challenges, and unique requirements of extra-examination and educational EQA programs.

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Introduction

This is Part I of a five-part series of articles describing the principles, practices and benefits of External Quality Assessment (EQA) of the clinical laboratory. Part I describes the historical, legal and ethical backgrounds of EQA and the properties of individual programs. Part II deals with key properties of EQA cycles [1]. Part III is focused on the characteristics of EQA samples [2]. Part IV summarizes the benefits for participant laboratories [3], and Part V addresses the broad benefits of EQA for stakeholders other than participants [4].

Medical laboratories and point-of-care testing (POCT) sites located around the world serve a critical role in medical care by providing objective evidence for disease diagnosis, prognosis, monitoring of development, and therapy success. They are expected to provide quality services and information characterized by accuracy, timeliness and reliability to their users, and must usually conform to national and international quality standards. Participation in External Quality Assessment (EQA) programs serves to monitor the quality of analytical and diagnostic services.

EQA is a procedure for interlaboratory comparison in which the analytical performance of participant laboratories is evaluated primarily using predetermined criteria. In each cycle, the EQA provider distributes samples with the same characteristics to participating laboratories simultaneously, giving them the conditions to achieve comparable analytical results. Within a specified period, participants analyze concentrations of measurands in or the properties of samples and submit quantitative, semi-quantitative (ordinal) and/or qualitative (nominal) results to the EQA provider. Target values are established either by Reference Measurement Procedures (RMP), by consensus of results obtained by expert laboratories, or by consensus of all reported results. The preparation of test material by adding a known amount of the measurand to a sample is less common; for details see Part II, chapter "*Determination of the target value*" [1]. Individual results are evaluated by comparison with the target (or assigned) value and the results of other laboratories, assessed against established analytical performance specifications for accuracy, and participants receive feedback on their performance. EQA programs usually consist of several individual cycles per year, and the number of samples in individual cycles varies depending on the provider. As required by ISO 15189:2022, they increasingly cover more phases of the entire laboratory examination process – from pre-examination to examination and post-examination - and allow laboratories the opportunity to identify weaknesses or potential errors in every single step of the examination process [5] (Figure 1).

EQA providers are impartial expert organizations that pursue either commercial or non-profit objectives. Their services cover far more than their name suggests: they not only organize and supervise EQA schemes, but they are also the point of contact for medical and technical enquiries. They also serve as a network center connecting laboratories, experts, health authorities and many more.

EQA programs and their providers play a crucial role in medical care, as they are quality partners to every discipline in medical laboratory diagnostics. By assessing the analytical performance of diagnostic laboratories, they not only support participant laboratories but also provide benefits for patients and their clinicians, for *in-vitro* diagnostics (IVD) manufacturers, the scientific community, regulators, notified bodies, accreditation bodies, national health organizations and policymakers, and public health authorities.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) guidelines define proficiency testing (PT) as *"laboratory performance evaluation for regulatory purposes"* and EQA as *"laboratory performance and method evaluation with a focus on education and support purposes"* [6]. Nevertheless, there is a lack of conformity amongst the practice community about the definitions of the terms "PT" and "EQA". They are mainly used interchangeably – maybe with a preference of "EQA" in Europe and "PT" in North America [7]. For purposes of this paper series, we use the term "EQA" to refer to all evaluation processes about interlaboratory comparison, as defined by the applicable standard ISO/IEC 17043:2023 [8].

Basics and general information about EQA

History of EQA

Though the US military conducted regular surveys of syphilis serology laboratory competence in the 1930s [9], the first published surveys of chemistry and hematology assays were in the late 1940s in the USA and the UK in the early 1950s [10, 11]. These demonstrated wide (2- to 4-fold) variation in results between laboratories, not attributable to the methods used, even with aqueous solutions containing the pure substance of interest, whereas in almost all cases there was no evidence of bias [10, 11]. Sporadic surveys, published and

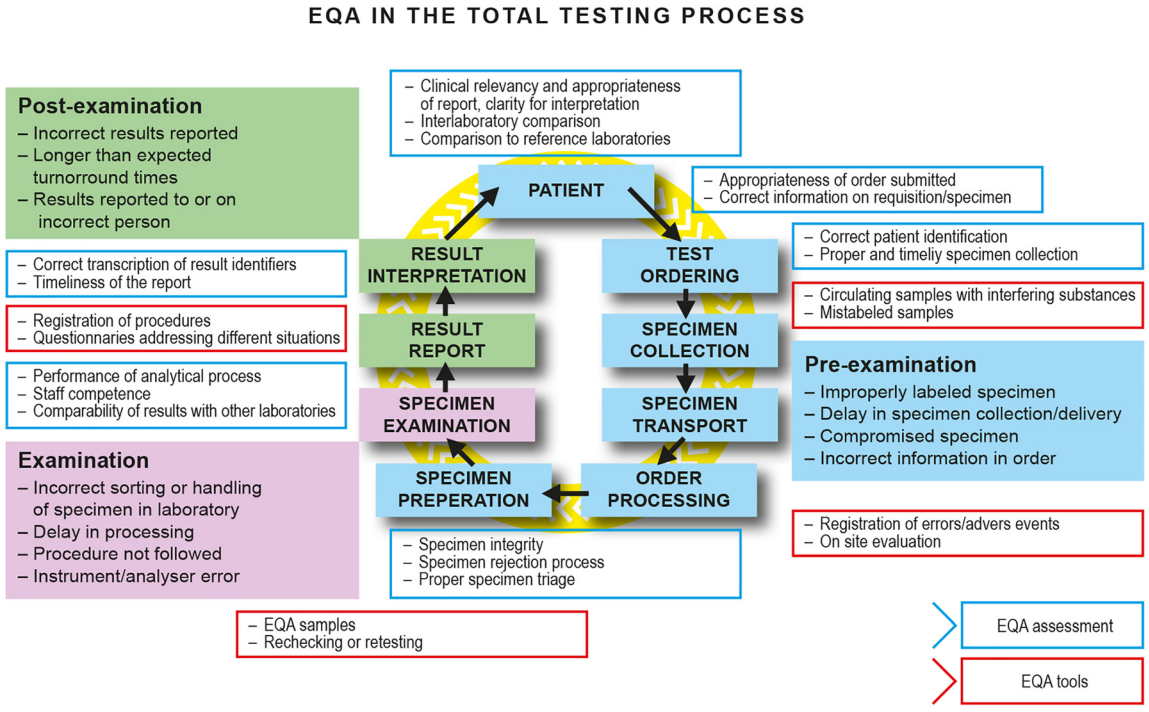

Figure 1: EQA in the total testing process. This schematic representation of the laboratory total testing process (TTP) shows the critical steps of the life cycle of a diagnostic test on a patient. Several processes take place before (pre-examination) and after (post-examination) the examination process. The process of EQA participation can help elucidate points in the TTP where error can occur, especially the value of EQA in the examination phase (pink boxes). The EQA process involves several steps along the TTP, shown as blue framed boxes "EQA assessment", while red framed "EQA tools" are that kinds of EQA that can be employed in addition to assessment of the examination process and which can help detect errors in the pre- and post-examination phase.

unpublished but too varied and numerous to reference, continued during the 1950s and 1960s, with similar findings. Most were geographically limited, in their scope in terms of analytes, especially in the challenges of producing reports within a meaningful timescale. These surveys were, however, instrumental in raising awareness of the need for quality assurance (QA) and stimulating the development of internal quality control (IQC) techniques adapted from the manufacturing industry [12, 13].

However sophisticated the application of IQC, it became obvious that EQA was essential to attaining and maintaining comparability of results among laboratories. This led to the establishment of national or regional programs in the USA [14], UK [15] and other countries in the late 1960s and early 1970s. EQA services then spread across further disciplines in laboratory medicine [16] and geography [17]. These took advantage of advances in data processing technology to provide timely reports, and emphasize the frequency of distributions, the number of analytes and specimen numbers. The ethos differed between countries, with some driven by legislative requirements (e.g. the Clinical Laboratory Improvement Act (CLIA) in the USA and the Calibration Law in West Germany) [18, 19]. Most, however, followed policies of voluntary participation with the aim of self-improvement based on scientific principles. Though program designs varied across countries, the objectives were to deliver regular services with frequent multi-specimen distributions and rapid feedback through reports, including scoring systems. However, some were restrained by the resources available from the government or the professional societies responsible for delivery [15].

There remained some confusion in terminology, however, as there was a misconception that external programs could provide an element of "control" despite their retrospective nature. This was dispelled by the publication of the outcome of a WHO Europe consensus conference [16, 20]. This clearly differentiated between the roles of the components of analytical quality assurance:

– IQC as the set of procedures undertaken for the continuous monitoring of laboratory operations and results, to decide whether the results are reliable enough to be released
– EQA as the system of objectively checking laboratory results by an external agency, including retrospective comparison of a laboratory's results with those of others, to establish between-laboratory comparability

It also outlined substantial agreement on desirable aspects of program design [16, 20]. By the mid-1980s national EQA

services had been established in many countries. Programs continued to develop in succeeding decades, increasing the scope of analytes surveyed and the sophistication of their designs in delivering information helpful to their participants in improving their performance [14].

Legal background to participation in EQA

A study on the impact of regulatory requirements on EQA failure rates shows that different countries have very different regulations and recommendations for participation in EQA schemes in general and the frequency of participation (Table 1) [21]. In most of the 33 countries reported in this regard, there is a clear legal obligation to participate in EQA; to a lesser extent, authorities or other official bodies, such as medical associations, review the participation and performance of individual laboratories in EQA or the EQA provider reports incorrect results to them; to a small extent there are (at least potential) sanctions of a financial nature or by restricting the authorization to carry out examinations with failed EQA (Table 1).

Financing of EQA programs

Providing an EQA service can be expensive due to the procurement of material, analysis of material, the need to verify stability and homogeneity, logistic issues both in sample production and dispatch as well as the support for educational activities to complement the EQA program. The funding source may, therefore, hinder what a particular program can offer and restrict the range of measurands or breadth of challenges.

EQA providers can be classified in terms of their funding as either not-for-profit, usually a professional/medical association or a government agency, or for-profit, usually a commercial organization. Mixed models, like foundation, medical association plus individual person ownership, government plus professional/medical association are also possible. What laboratories pay and if they have a choice of provider can also vary by country and depends on whether or not a government agency, a not-for-profit organization or a commercial company provide the EQA. In many countries, EQA participation is mandatory (Table 1).

There are also fundamental differences in classifying EQA providers on the basis of whether they are regulatory or educational. These include if they provide programs outside their country of origin, the ownership (professional

Table 1: National regulations on EQA participation.

Country	EQA participation required by law	Authorities informed about incorrect results	(Impending) financial consequences of EQA performance[a]
Australia	Yes	Yes	Yes
Austria	Yes	No	No
Belgium	Yes	Yes	Yes
Brazil	Yes	Yes	No
Canada	Yes	Yes	[b]
Chile	Yes	Yes	No
Croatia	Yes	No	No
Czech Republic	No	No	[b]
Estonia	Yes	No	No
Finland	No/yes[c]	No	No
France	Yes	Yes	Yes
Germany	Yes	Yes	Yes
Greece	Yes	No	No
Hungary	Yes	No	No
India	No	No	No
Ireland	No	No	No
Italy	Yes	[b]	No
South Korea	No	No	No
Lithuania	Yes	No	No
Malaysia	Yes	No	No
Mexico	No	[b]	[b]
Norway	No	No	No
Netherlands	No	No	No
Romania	No	No	No
Saudi Arabia	Yes	No	[b]
Slovak Republic	Yes	Yes	Yes
South-Africa	Yes	No	No
Spain	No	No	No
Sweden	No	No	No
Switzerland	Yes	No	No
Thailand	No	Yes	No
Turkey	Yes	No	[b]
United Kingdom	No	Yes[d]	No
USA	Yes	Yes	Yes

Adapted from Buchta et al. [13]. [a]Financial consequences means, for example, the further approval/withdrawal of approval to carry out analyses or the continuation/suspension of reimbursement depending *directly* on participation and/or performance in EQA. If, on the other hand, accreditation according to ISO 15189 is a prerequisite for reimbursement and participation in EQA is not required by law but by ISO 15189, EQA participation is *indirectly* economically required by the client, but this does not count here as financial consequences based on legal conditions. [b]Data not available/not uniform throughout the country. [c]In Finland, approval is needed by the Regional State Administrative Agencies to perform laboratory diagnostics of infectious diseases, and it includes mandatory participation in EQA programs for each examination procedure used. [d]It is not mandatory for EQA providers to escalate poor performance.

organization, private), type of organization (not-for-profit or for-profit), the range of programs they offer by discipline, measurand, and the level of support they provide to their participants. For an EQA provider to be sustainable it must be able to finance all activities within its goals fully. These include all resources – personnel and material requirements – for program delivery and customer support activities such as education and troubleshooting assistance.

Sources of income may include subscription fees for programs and income from additional material, income from webinars and conferences, grants and, in some cases, direct financial support from the government.

For some EQA organizations, lack of sufficient funding constrains the development and structure of EQA programs. Funding also influences the educational activities that can be provided and the cost to participants. The ability to provide verifiable commutable material or to have reference method target value assignment may be limited because of the funding model.

EQA and ethics

The introduction of personalized medicine requires laboratory medicine to enter the era of precision diagnostics, setting clinical performance specifications to develop and evaluate assays for clinical use [22]. It is the role and ethical obligation of EQA providers to employ contemporary methods that can identify examination procedures capable of meeting analytical performance specifications, and to enable laboratories to determine whether they meet these requirements and whether the analytical service is beneficial for the patient. The applicable standards refer to ethical requirements for the laboratory towards its patients and the EQA scheme provider towards its participants in points 4.1 “Impartiality” and 4.2 “Confidentiality” of ISO 15189:2022 and ISO 17043:2023 and for the laboratory additionally in 4.3 “Requirements for patients” of ISO 15189:2022 [5, 8].

EQA programs play a pivotal role in assessing laboratory performance through standardized evaluations. They provide uniform samples and compare results across institutions, ensuring consistency, accuracy, and reliability of laboratory test results. This assurance is critical for patient outcomes, reinforcing their safety and instilling confidence in the healthcare system.

Ethical participation in EQA programs highlights a laboratory’s commitment to fundamental principles such as patient safety, transparency, accountability, and professional integrity. It ensures that laboratories identify and rectify errors, continuously improve their testing procedures, and adapt to advancements in medical technologies. For instance, as new diagnostic tools and techniques emerge, EQA programs update their standards and evaluations to ensure that laboratories use the most effective and accurate methods. This commitment enhances the quality of patient care and strengthens public trust in the healthcare system.

Confidentiality is a cornerstone of ethical consideration in EQA programs. It ensures the secure handling of patient information and laboratory performance data, reassuring patients, healthcare providers, and laboratories about protecting their data. Ethical practices demand that patient samples and EQA results be protected from misuse, fostering trust among all stakeholders.

Thus, EQA programs are not just a technical necessity but an ethical imperative. They play a vital role in safeguarding patient outcomes, reinforcing public trust, and encouraging continuous learning and quality improvement within laboratories, making them indispensable to modern healthcare [23].

Information management systems in EQA

EQA requires software with various functionalities to manage and administer programs and participants effectively. This functionality may be provided by bespoke development or commercial solutions as a single system or by multiple systems connected to perform specific tasks. Information systems used by EQA providers should be validated to ensure that they are fit for purpose and operate as intended. Data integrity must be ensured, data manipulation or loss must be prevented, and the accuracy of test results must be maintained. To ensure that detailed audit trails, role-based access control, and regular, verified data backups are just as required as redundant systems and infrastructure with regular monitoring and proactive maintenance to prevent disruptions and ensure continuous data access to authorized users. Additionally, as the software may be accessible from the internet for data entry and can also be interfaced with external laboratory information systems (LIS), robust cyber security measures are essential to protect data and systems from malicious attacks, threats, and breaches. Since the structure of software for EQA also provides a good overview of processes running in parallel, software features generally required for most EQA programs are listed in Table 2.

Regulatory and educational/aspirational purposes of EQA

EQA serves different purposes, namely regulatory and educational/aspirational [6, 24]. While the primary

Table 2: Characteristics and modules of software for EQA.

The software should-

Regarding **participant management**

- Have features to securely manage participant information, demographics, contact details, and history.
- Enable enrolment in EQA programs and cycles and provide tracking and communication with participants.
- Have processes to manage general data protection regulation (GDPR) and privacy requests from other jurisdictions.
- Enable redaction or deletion if required.

Regarding **specimen management**

- Provide a mechanism to track specimens from collection through storage and assignment to an EQA cycle.
- Link homogeneity testing data to the specimens assigned to a program so that they are identified in the event of specimen integrity issues.
- Also link safety testing results to the specimen, and sample dispatch should be prevented unless safety testing is complete and the samples have passed.
- Also manage the homogeneity testing schedule and randomization of the samples tested.

Regarding **test design and management**

- Allow the creation and management of test items/questions.
- Support the display of patient history and demographics, different question formats, scoring mechanisms, embedded multimedia, and the ability to generate customized request forms for each participant.
- Allow measurands for each sample/cycle to have assigned values set and enable multi-level assessment criteria, including fixed and percentage measurements depending on the measurand concentration.

Regarding **cycle notification**

- Provide a platform to notify participants of open EQA cycles and provide reminders if results for a cycle have not been submitted.
- Allow participants to access functionality to track specimen delivery and view and print sample storage, handling, preparation and submission instructions.

Regarding **result collection**

- Accurately capture analytical methodology and default the methodology and units of measure whenever possible.
- Enforce appropriate decimal precision, where results are entered using a web interface or electronic form and consideration should be given to allow customization of the form to match the result sequence of the analyser or LIS to reduce errors.
- Provide feedback that results were successfully submitted and allow the participant to view a summary of submitted results and a history of any alterations made.
- Include a mechanism to ensure acknowledgment of successful electronic submission and a notification if an electronic submission has failed or results have not been submitted.
- Allow the review of electronic submissions and maintain an audit trail.

Regarding **result analysis**

- Securely store examination results and provide an audit trail of activity taken against a result.
- Provide appropriate unit conversion and offer robust data analysis tools to generate statistical reports, perform analysis, identify trends, and measure participant performance against the defined allowable limits of performance.
- Display outliers to the EQA staff analyzing the data and provide real-time feedback to the group statistics where outliers are included or excluded.
- Make an individual participant's previous performance available during the result analysis.

Regarding **result reporting**

- Be able to generate comprehensive and customizable reports for individual participants and specific groups, including manufacturers. These reports may include performance summaries, scores, graphical representations, and feedback on areas of improvement.
- Enable accessibility where color is used in either web or printed reports.
- Have the ability to track report versions at a participant level and should be able to re-issue amended reports at a participant or program level.
- Be able to display the reason for the amendment and what was amended.

Regarding **communication and collaboration**

- Facilitate effective communication between the EQA provider, participants, and relevant stakeholders. This may include features like email notifications, dashboards, browser or text messaging systems, and discussion forums.
- Allow participants to opt out in accordance with relevant privacy legislation.

Regarding **security management**

- Be able to protect against unauthorized access, data breaches and cyber threats. This can be achieved by robust authentication methods (multi-factor authentication for all user accounts), strong access controls, encryption protocols, continuous monitoring, automated backups and disaster recovery plans. Encrypting data ensures that even if accessed without authorization, they remain unintelligible. As shared infrastructure risks in multi-tenant cloud environments can lead to data leakage, using virtual private clouds (VPCs) and network segmentation can help to isolate sensitive EQA workloads.

Regarding **audit trail and compliance**

- Maintain an audit trail of activities and changes made within the system.
- Support compliance with relevant accreditation standards, including ISO/IEC 17043, jurisdiction regulatory requirements, and industry best practices.

Regarding **user support and training**

- Be comprehensively documented, including user guides and training materials for EQA staff and participants. These guides should be made available at the point of use, and technical support should be available to address issues or questions that may arise.

regulatory purpose is to identify poorly performing laboratories, the leading educational/aspirational purpose of EQA is to improve the quality of laboratory examination. Regulatory EQA activities usually have wide tolerance limits, whereas for educational EQA activities, these are generally tighter and may be based on clinical outcome data, biological variation or "state of the art" [25]. EQA programs may offer combinations of performance specifications that relate to either regulatory or educational/aspirational aims. Because of the different analytical performance specifications, a laboratory can have acceptable performance in one

(regulatory) challenge and unacceptable performance in another (educational) for the same measurand.

EQA for regulatory purposes

The primary purpose of challenges intended for regulatory purposes is to identify poorly performing laboratories, and this can shape the design of the EQA program (e.g., the number of samples, the frequency of the EQA cycles and the performance expectations [25]. Laboratories that persistently are outside acceptance limits will usually receive some form of punitive outcome in the form of external inspection or loss of public funding. Using broad acceptance criteria ensures most laboratories do meet the required criteria. Furthermore, failure to achieve these criteria may result in significant consequences for the laboratory's license to practice. These criteria may include compliance with international standards such as ISO 15189:2022 and/or superseding national guidelines and laws such as those determined by a nation's quality regulators, e.g. CLIA in the USA [18] or the Guidelines of the German Federal Medical Society for the Quality Assurance of Laboratory Medical Examinations (RiliBÄK) [26]. The RiliBÄK stipulates that reimbursement for laboratories that fail consecutive EQA cycles for the same measurand is suspended until the assessment is successfully passed again in a subsequent cycle. The responsible third-party payers execute the suspension of reimbursement. With a mandatory program, there may be unintended consequences on sample handling such as laboratories treating these EQA specimens differently from patient specimens to ensure acceptable performance. Though these programs may be perceived as more stable, they may not be adaptable to meet the evolving needs of the profession [27].

EQA for educational purposes

The second purpose of EQA programs, best described as 'aspirational' or 'educational', is to improve the quality of laboratory examination through the provision of educational and scientific principles and sometimes research input as well as the assessment of regular EQA samples.

This distinction from wholly regulatory programs encourages the inclusion of more challenging samples (e.g. extreme concentrations to challenge the limit of detection, presence of interfering substances to challenge assay selectivity, rare microorganisms to assess the competence of the laboratory staff in this regard) and sometimes more stringent acceptance limits. This comes with an increased risk of 'failure' and emphasizes the improvement of both individual and collective laboratory performance through the sharing of best practices. Within the laboratory, EQA provides an essential educational function through the review of reports (especially those with educational commentary or extended educational content integrated into a traditional EQA program), the use of EQA cases (e.g. in morphology) for staff training and competency assessment, reflection on performance in seminars and training sessions and support from the EQA provider to troubleshoot nonconformances [27]. The EQA provider may publish data and questionnaire responses from the EQA program, evaluating the state of the art in performance and shaping best laboratory practices. Some countries have a formal EQA oversight structure and mechanisms to share best practices for patient safety.

Many EQA programs occasionally distribute samples that are primarily for educational purposes and may be excluded from regular performance assessment. These might include interfering substances (e.g. glucose in creatinine assay, heterophilic antibodies in immunoassays) intended to identify differences in selectivity between methods or IVDs.

In recent years, EQA programs with an exclusive educational focus have been established to supplement traditional services. These may assess the performance of an individual practitioner or provide competency assessment and/or continuous professional development (CPD) activities for laboratory professionals.

The organization and design of educational programs are varied, and the laboratory must consider the most appropriate program to support their needs. This is particularly true when the laboratory wishes to enroll a staff team for competency or professional development, in which case an effective management interface is essential for registration and monitoring the staff compliance. Programs that encourage or allow group registration by an employer are highly effective in terms of staff engagement, since the employer takes the responsibility for payment and management. Educational programs may include interpretive case studies, in which each participant views the same case with a patient scenario and patient results; morphology skills-based programs; guideline-based case generation, where each participant receives different cases generated by artificial intelligence etc. Where guidelines are established and effective, e.g. in blood transfusion practice, performance evaluation against guidelines is an unambiguous performance comparator; however, this may provide challenges where guidelines differ regionally or nationally.

Without rigorous professional guidelines, the provider must consider how the 'correct' answer is determined. It is relatively straightforward to assess the participant's response against the whole participant group and even to rank the participant on that basis. However, this type of analysis may be overly simplistic: firstly, the program should ideally provide a peer group-related performance

assessment to reflect the different levels of experience in the participants and, secondly, it should be recognized that the most common response may not be the most clinically significant. The provision of an expert commentary or performance assessment by an expert panel of assessors gives a more effective educational outcome. Where the performance of the individual participant is scored against an expert answer or by an expert panel, the expert panel and markers must have a demonstrated track record in the field, maintain their professional accreditation and mark the participants' responses against objective criteria [28]. Other features of the program design to consider are whether the cases remain open indefinitely as a library or bank of cases or have a closing and reporting schedule; whether participants are allowed single or multiple attempts at the cases; the complexity and range of cases provided and whether this is indicated; whether the program encourages reflection on what has been learnt from the cycle; whether resources informing the case are all made available with the case presentation or released in a staged fashion.

EQA programs

The life cycle of an EQA program

All EQA programs have to start somewhere. Once established, the EQA program usually operates on a continuous basis, and on rare occasions, a program is terminated. Whether the EQA service is pre-examination, examination or post-examination, or requires the distribution of physical specimens, or covers derived examinations based on analytical results and an algorithm, EQA service providers are continually looking to expand and improve their services to meet the needs of their users better. Providers' development and implementation of EQA programs is an intentional undertaking requiring significant resources, considerable research and development, and follows a stepwise process, as illustrated in Figure 2.

Conception

EQA programs are born from a multitude of routes. These include feedback from service users/other stakeholders, EQA provider horizon scanning etc. However, there needs to be a demand that can be derived from different reasons (Table 3) Once the requirement for an EQA program is in place, the EQA provider needs to ensure that it has both the scientific and technical capabilities to design, grow and then maintain the EQA service.

The scientific and/or technical expertise could be provided by external scientific advisors or steering committees, or it could be subcontracted. Program design and evaluation (performance assessment) remain the responsibility of the program organizer and cannot be subcontracted. This is a requirement to ensure compliance with ISO/IEC 17043:2023.

Program design

Good program design is crucial for an effective EQA program. Many factors contribute to this, including but not limited to the type of material that will be distributed, the number of specimens, frequency of specimens, concentration range that will be covered, assigned values, scoring systems, report design etc. Each program will be overseen by and be the responsibility of a program organizer. EQA program design is an area that is not covered in depth in ISO/IEC 17043:2023, nor is it an area that is harmonized between different EQA providers offering EQA services for the same measurand [8]. This variation in design does allow laboratories the option to participate in EQA programs that suit their needs; however, it is up to the participant to review the program design of each provider to ensure that they meet the requirements as a supplier for the clinical services that are provided at an individual participant's laboratory.

Based on experience, for EQA to be effective, participants must have confidence in the program design. This can

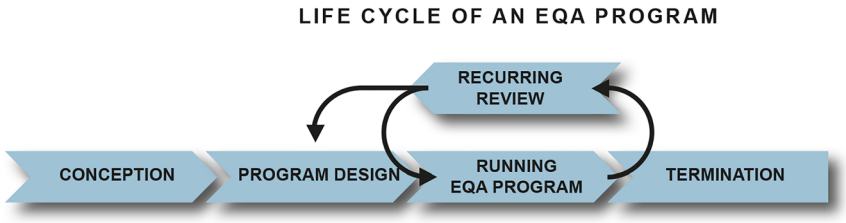

Figure 2: Life cycle of an EQA program. After conception and design, an EQA program comes into its routine run. Ongoing programs regularly present challenges to registered participants in the form of EQA cycles. The performance of individual EQA programs is evaluated on a regular basis and, if necessary, details of programs are adapted to match the needs of participants and technology. However, an EQA program may also reach the end of its life cycle, either because the included measurands have lost their clinical relevance or because the EQA provider decides to close it for various reasons.

Table 3: Reasons to initiate or terminate an EQA program.

Initiation of a new or adapted EQA program	Termination of an EQA program
– Development of a new biomarker – as was the case for SARS antigen and antibody detection – Change in examination procedure's usage or application that may require a more regular and structured EQA program than basic interlaboratory comparisons – An EQA provider looking to expand their repertoire of the services that they provide, which could be for well-established examination procedures that they don't yet cover, or enhance their existing EQA programs – Government requirement	– The measurand is no longer required by clinicians, or is replaced by another service. – It may not be viable for the EQA provider to continue providing the service. This could be due to insufficient numbers of participants or the EQA provider not being able to acquire relevant material to prepare samples. In this case the EQA provider will work as much as possible with laboratories to maintain the service, either with collection of material, or in some cases can support a simple specimen exchange program for interlaboratory comparisons, or cooperate with other EQA providers – The EQA provider may wish to consolidate services either in-house or with another EQA provider – An EQA provider may terminate a scheme in the case where a joint decision was made that other EQA providers are better suited to handle this scheme. In some countries, the different EQA providers have specialties shared between them so that all providers do not need to cover all measurands

Table 4: Requirements and success factors of EQA programs.

(1)	**Samples that**
	– Are as close as practicable in composition to clinical specimens
	– Cover clinically relevant concentrations
	– Are stable and homogeneous
	– Are probing for the assay system i.e. contain interferents
(2)	**An appropriate basis for assessment, through**
	– Reliable and valid assigned values
	– Robust statistics and scoring criteria
(3)	**Effective communication of performance data, using**
	– Structured, informative and intelligible reports
	– A running scoring system
(4)	**Sufficient recent data from**
	– Adequately frequent distributions
	– Timely feedback of information

Adapted from [19].

be achieved by providing information on key data and facts as shown in Table 4. Though all evidence of the effectiveness of EQA is necessarily circumstantial, these principles have been tested through changes in program design [29].

Growth, development and maintenance

An EQA program may start as a simple survey of practice and incorporate some EQA samples, followed by a pilot phase that may run for several cycles. This allows both the EQA provider and the participants to fine-tune the design before the EQA program enters routine operation. More experienced EQA providers may launch an EQA program based on their existing experience and infrastructure for delivering EQA services. The growth of EQA programs occurs in terms of the number of participants, the number of analytes assessed in them, or the information collected and reported, both for the participants and for other stakeholders [3, 4]. The amount of sample material that is to be prepared for a large number of participants can certainly be a challenge, especially if it increases quickly and unexpectedly, since many materials need long time for production and characterization, and others are based on clinical samples that are only limited available. For the further development of EQA programs, both the proposals and expectations of the participants can be decisive, as well as changes in clinical practices, such as the replacement of established analytes through new ones.

Evaluation of programs

EQA is more than an assessment of a laboratory's performance, it also has the potential to offer post-market surveillance, provided that some prerequisites are met. At the cycle's close, the program organizer/EQA provider will review the overall performance of all methodologies. Changes in performance and/or changes in market/clinical requirements may lead to the adaptation of the EQA services by the EQA provider or discussions between the EQA provider and IVD manufacturers. Depending on the nature and extent of the issue, and local/national regulations, the EQA provider may be required to take further action. These actions may relate to all areas of the design of EQA programs, e.g. the intended purpose of the EQA scheme, test systems allowed to participate (cave commutability!), the characteristics of the materials used and the conditions to which they may be exposed during transport to the participants, the method of setting the target and the acceptance criteria for the results obtained and reported by the participants.

Significant changes to EQA program design may not be covered under the scope of an EQA provider's ISO/IEC 17043:2023 accreditation. Further assessment may be required by their local accreditation body. EQA program review and development are all part of ongoing quality improvement.

Termination

The EQA program design may evolve over the program's lifetime, but in some cases, the EQA program may need to be finalized. Several factors can cause the provider to discontinue an EQA program, like measurands no longer required by clinicians, or impossibility to acquire appropriate EQA materials (Table 3).

In all cases where an EQA program is coming to an end, there will be processes that need to be followed to ensure that all relevant stakeholders, including participants, suppliers, the accreditation body etc., are informed. The end of an EQA program is a time for reflection on how EQA has supported the provision of specific services and what can be learnt and utilized for future programs.

Frequency and intensity of EQA

Apart from the Rilibäk, which regulates the minimum frequency of participation in EQA schemes for laboratories in Germany, there are only a few other guidelines regarding frequency and intensity of EQA [27]. For example, concerning screening of donated blood for transfusion-transmissible infections (at least two cycles per year [30]) or blood lead (three samples every two months [31]). One of the reasons for a lack of harmonization in this area is that ISO 15189:2022 suggests that EQA providers should be accredited in compliance with ISO/IEC 17043:2023, which specifies the criteria and procedures the EQA providers are to follow [32]. The choice of frequency by the EQA organization may be influenced by existing information regarding results accuracy and/or harmonization, the availability and price of control materials and the cost of the examination in laboratories. Consequently, EQA providers design their programs with different frequencies of cycles [33].

Laboratories are ultimately responsible for deciding which EQA program they use for their service. The laboratory should take into account the type of service that they are providing (prognosis, diagnosis, screening), the prevalence of the disease and the number of investigations undertaken by the laboratory (workload), the analytical complexity, the error rate of the investigation and the specialist nature of the investigation [34]. The laboratory can then choose an EQA program that meets these requirements. A review of 22 organizations representing 407 programs showed that the median for all examined disciplines was four cycles per year. The responses of this survey were categorized into scientific disciplines, i.e. biochemistry (6 cycles per year median), hematology (three cycles per year median), hemostasis (4 cycles per year median), and microbiology (median three cycles per year). As the authors concluded, the number of EQA cycles (and number of samples) varied widely per year within and between each discipline. Furthermore, there is a consensus that error rates and testing volume play an essential role in establishing the frequency of EQAs [34].

One study has tried to develop a framework for evaluating the frequency of EQA challenges [35]. The aim was to demonstrate the impact of the correlation of EQA data between different samples on the information that can be extracted from EQA results, such as the evaluation of laboratory or method performance. It was shown that the assessment of performance was flawed by the presence of a correlation between EQA results from different samples. Therefore it becomes less beneficial to send more samples per EQA cycle or organize more EQA cycles within a time interval. The authors concluded that there will always be a tension between resources (cost of the program, time to run and analyze the results) and value of appropriate intervention on problems that may increase the risk to patients [35].

The "ideal" frequency of EQA in the context of medical laboratories can vary greatly depending on the specific service a laboratory provides [36]. Both a higher and a lower number of individual samples per cycle seem to have advantages and disadvantages (Table 5). While a higher frequency seems to have more advantages in terms of analytical quality, the advantages of lower frequencies are more economical. The disadvantages seem to be the other way around [35].

Extra-analytic EQA

ISO 15189:2022 requires that the EQA program selected by the laboratory be used to check pre-examination, examination and post-examination processes [5]. Although most errors happen within the pre-examination and post-examination processes, far less emphasis has been put on their quality control and improvement, compared to the analytical parts [36]. The reason might be that pre- and post-examination processes can appear to be particularly hard to control since, contrary to the analytical phase, most steps occur outside of the laboratory.

Another issue with regard to pre-examination and post-examination quality control are difficulties in the

Table 5: Advantages of higher and lower frequency and intensity of EQA.

Advantages of higher frequency and intensity	Advantages of lower frequency and intensity
– A broader range of sample concentrations that might allow testing at extremes of clinical need or specific scientific studies – Improved reliability of the statistical assessment of assay performance components at the end of an EQA cycle – Earlier assessment of corrective actions – Potentially fewer patients that are affected by undetected changes in assay performance – Allows inclusion of 'educational' samples without disrupting routine assessment	– Reduced costs due to reduced prices of programs – Reduced reagent costs – Reduced cost due to reduced time in handling EQA results – Reduced costs to EQA organizers – Suitable in the event of supply difficulties (rare materials)

acquiring and documenting of such errors and the lack of universally standardized quality indicators (QIs) for evaluating, monitoring and improving these steps within the total testing process [37]. Several organizations provide information and platforms for QI acquisition, documentation and benchmarking [38, 39]. Many existing laboratory information systems (LIS) do not come with a pre-built functionality of recording QIs, making this process partly/mostly a manual one (which is both time consuming and error prone); however, LIS are constantly improving, so potentially, data collection will be easier. Additionally, current coding systems, such as the Logical Observation Identifiers Names and Codes (LOINC) [40] or the Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) [41] are focused on intra-laboratory (analytical) processes and initiatives like the Standard Preanalytical Code (SPREC) [42] systems are currently used only for biobanking purposes. This makes extra-analytic quality benchmarking intentions almost impossible. Finally, no acceptance criteria have been defined for most – if not all - extra-analytical QIs, leaving laboratories collecting and documenting such data to evaluate them like they would do with an IQC by looking out for drifts and variations of recordings over time.

Currently, most EQA providers who provide pre-examination programs are either 1) surveying the procedure and checking the knowledge of participating laboratories or 2) sending out samples designed to test pre-examination systems (e.g. for serum indices detection, RNA/DNA extraction, etc.), or pre-examination case-reports with either real or fictional data [43–46]. Recently, a new type of EQA program has been introduced, aimed at improving/maintaining quality of samples sent to the laboratory via pneumatic tube transport [47–49]. Post-examination data may be collected within examination EQA programs by asking for interpretation of reported results, collection of reference interval information or answering a series of case study questions.

Pre-examination and post-examination programs are designed to look specifically at QIs not only facing challenges with data collection, but also evaluating data and reporting meaningful information back to laboratories. A number of EQA providers use a sigma metric approach. A risk-based scoring system allows laboratories to prioritize action.

Developing specific EQA programs for each extra-analytic error possibility seems unfeasible [50]. Nevertheless, such programs are vital for quality maintenance and improvement. Therefore, it seems reasonable to focus on extra-analytical errors with the highest frequency and/or patient safety risk while considering their applicability. An alternative could be a mandatory constant documentation of selected QIs. Although no QIs are specifically mentioned, the ISO 15189:2022 standard stipulates that pre- and post-examination QIs should be regularly recorded, documented and evaluated. Currently, most laboratories are collecting information on only a few QIs, if any [36, 51, 52], demonstrating once more that there is room for improvement regarding quality management of the extra-analytical phases.

In some cases, it is possible to combine pre-analytical, analytical and post-analytical EQAs where case reports together with control material are circulated, and both pre-analytical, analytical and post-analytical responses are registered, ending up with a diagnosis and how this is reported to the clinicians. This is often done for rare diseases [53].

Patient-based EQA programs as a supplement to traditional EQA

Patient based quality control programs can be used both as an IQC program and as a supplement to EQA. An emphasis on the last approach will be given here. A patient-based EQA program can be defined as an EQA program asking for statistical parameters of measurements from a defined patient population. A Patient-Based EQA program shares similarities with Patient-Based (internal) Real-Time Quality Control programs [54]. Setting up a patient-based EQA program is perceived as a complex and challenging task. The most important factors are the ability of laboratories to

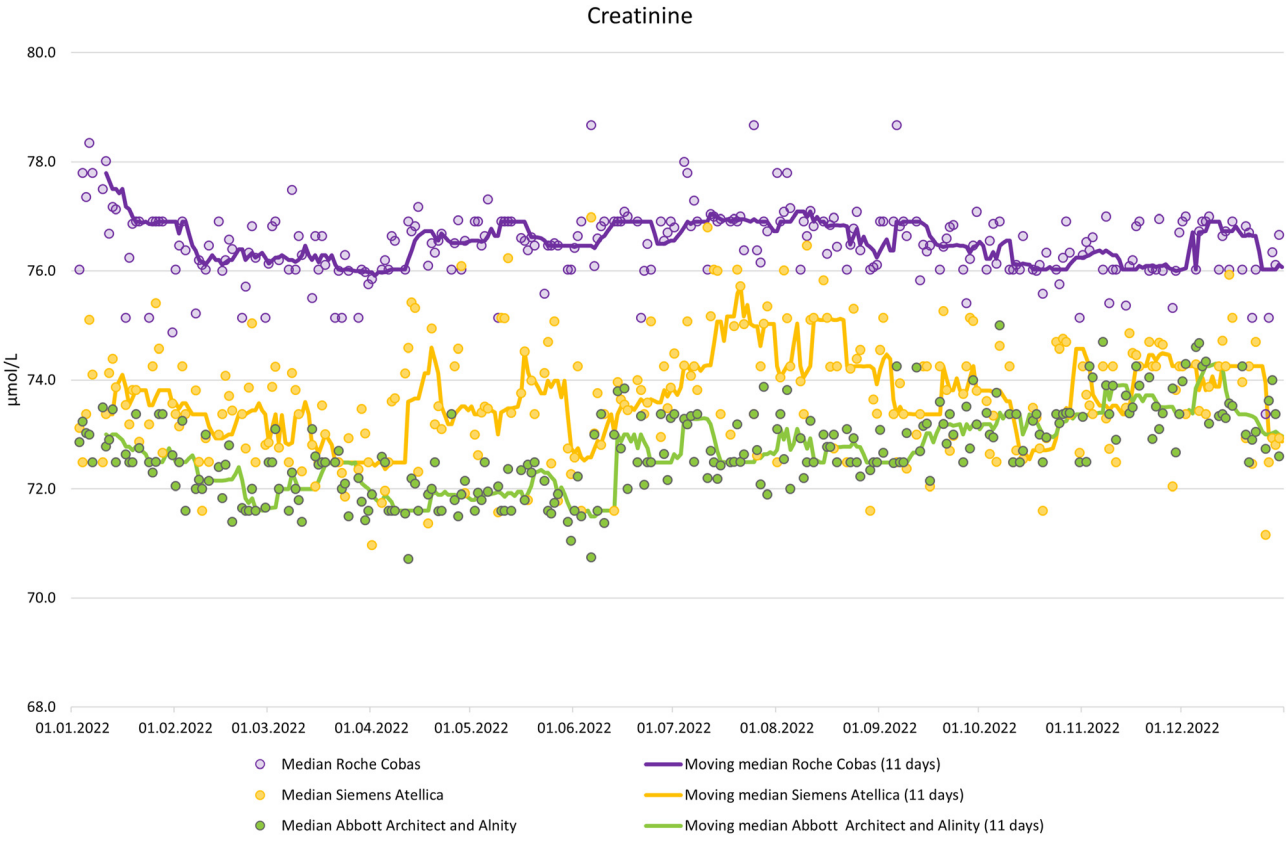

Figure 3: Example on results of a patient-based EQA program for creatinine. This example illustrates a patient-based program where laboratories report daily medians calculated from all results for an outpatient population. The results are grouped according to the instrument used. The date is on the x-axis and the y-axis shows the concentration of the measurand. The dots represent the daily creatinine medians calculated from all instruments in the same MP group. The lines are the moving medians for the creatinine MPs calculated from the last 11 medians. The overall median for the Roche Cobas group is 76.6 µmol/L (n=59847), Siemens Atellica 73.4 µmol/L (n=4620) and Abbott Architect and Alinity 72.5 µmol/L (n=14885).

transfer and send data to the EQA provider, the patient population from which the parameters are calculated, knowledge of pre-analytical factors, methods- and instruments, the analyte in question, and calculations, diagrams, and alarms or warnings. The main reason for setting up a patient-based EQA program is the shortcomings of regular EQA programs, mainly the lack of commutability or the lack of testing for commutability of many materials distributed in regular EQA programs [55, 56]. When the EQA provider supports automatic result reporting and the laboratory can generate and send reports automatically, a patient-based EQA program can become less labor-intensive and more cost-effective compared to conventional EQA programs. The primary effort for the laboratory lies in preparing the report and establishing the routine for automatic reporting.

Several techniques can be used for a patient-based quality control program, and examples of parameters are the average of normal (AoN), moving average (MA) and the moving median [57]. As far as possible, the chosen parameter should not be affected by the variation normally found in the selected patient population, and the chosen statistical approach should filter out noise. Usually, the purposes of a patient-based EQA programs are i) to monitor the performance of the examination procedure of the laboratory ii) to compare the results between laboratories using the same examination and iii) to illustrate equivalence between different examination procedures. Examples that can affect the performance of the examination procedure over time are the lot-to-lot variation for reagents and calibrators and reagent stability.

The rationale behind using patient specimens as EQA [58, 59] is that population-based parameters such as the AoN, moving average (MA) or moving medians for a defined patient population, e.g., the out-patient population, typically are stable over time, and any change is usually due to pre-analytical or analytical instability or error. If all pre-analytical and patient-related factors are known and equivalent, monitoring the population-based parameters for an instrument group or a method can be useful to verify

comparability between different measurement procedures (MPs).

A program based on patient results is sensitive to many factors, and when results are interpreted, many variables can affect the interpretation [58, 60, 61]. To optimize the outcome of a program based on e.g. patient medians, it might be necessary to take the pre-analytical factors into consideration when results are grouped, for example, it can be useful to register if the laboratory results are from fasting or non-fasting patients and if the sample material is serum or plasma. If there is a worldwide participation, the lifestyle and diet of patients from which the patient medians are calculated vary. For some analytes, it adds value to group results according to country or geographical regions [6].

As for conventional EQA programs, the performance limits are determined and set by the EQA provider, but a patient-based EQA program can't be used to establish the trueness for a MP, but only the equivalence between MPs. The quality of the EQA program depends on the laboratory reported data, the group size, and the method- and instrument grouping, and an optimized version of a patient-based EQA program can be an essential tool for surveillance and for monitoring the outcome of ongoing harmonization and standardization work. An example based on results from a patient-based EQA program [62] is given in Figure 3, showing the daily median and the moving median for different IVD medical devices (IVD-MD) based on results reported to the program during 2022.

Conclusions

EQA has been routinely available and covers many laboratory functions for over 50 years. Though the core principles have remained the same over this time, the EQA profession has and continues to evolve to meet the needs of the participants. EQA is a critical component within a laboratory's quality management system. It is incumbent on EQA providers to ensure that laboratories are fully aware of the information they have available to them so that they understand what they are participating in.

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